PET findings and neuropsychological deficits in a case of Fahr’s disease

Albrecht Hempel\textsuperscript{a,*}, Marcus Henze\textsuperscript{b}, Christopher Berghoff\textsuperscript{a}, Nohazarahit Garcia\textsuperscript{a}, Reinhard Ody\textsuperscript{c}, Johannes Schröder\textsuperscript{a}

\textsuperscript{a} Department of Psychiatry, University of Heidelberg, Voßstr. 2, D-69115 Heidelberg, Germany
\textsuperscript{b} Clinical Cooperation Unit, Nuclear Medicine, German Cancer Research Center and University of Heidelberg, Germany
\textsuperscript{c} Department of Psychiatry, Marien-Hospital, Euskirchen, Germany

Received 25 September 2000; received in revised form 7 August 2001; accepted 19 August 2001

Abstract

In a case of Fahr’s disease with frontal lobe type dementia and hyperkinetic-hypotone syndrome, functional changes were investigated using positron emission tomography (PET) with \(^{18}\)F-fluorodeoxyglucose (FDG) as a tracer. Computed tomography showed bilateral calcifications in the putamen and globus pallidus consistent with the diagnosis of Fahr’s disease and a frontally pronounced brain atrophy. In contrast, reduced glucose uptake in PET was not only confined to the areas mentioned above, but extended to the temporal and parietal cortices, bilaterally. These functional changes corresponded to the neuropsychological deficits observed, i.e. disturbed selective attention and cognitive flexibility, verbal perseverations, and declarative memory deficits. It is suggested that functional changes may precede cerebral atrophy in Fahr’s disease and may reflect deficits in functional circuits, which involve both the basal ganglia and the frontal, parietal, and temporal lobes. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Positron emission tomography (PET); Idiopathic basal ganglia calcification; Frontal lobe

1. Introduction

Idiopathic basal ganglia calcification or Fahr’s disease (Fahr, 1930) is a rare neurodegenerative disorder characterized by extrapyramidal motor signs, dementia and organic psychosis (König and Haller, 1984; Trautner et al., 1988). Clinical diagnosis is facilitated by the presence of bilateral calcifications in the basal ganglia in computed tomography (CT). These calcifications cannot be explained by any particular disorder of the calcium–phosphorus metabolism or other diseases involving the basal ganglia like toxoplasmosis, tuberous sclerosis, myotonic muscular dystrophy, idiopathic hemochromatosis, or mitochondrial encephalopathies. In a post-mortem histopathological and electron microscopic study (Kobayashi et al., 1987), calcifications were found bilaterally in
the basal ganglia, cerebral cortex, and cerebellum. Calcium deposits were also described in the adventitial cells of blood vessels. Apart from the calcaeous deposition of Fahr’s type in the basal ganglia, an atrophy of the temporal and frontal lobes was observed (Shibayama et al., 1992).

Numerous patients present a familiar trait with autosomal dominant transmission. Recently, a locus on chromosome 14q was identified in a family with dominant transmission of Fahr’s disease (Geschwind et al., 1999).

In a CT study involving 62 patients, Taxer et al. (1986) found the extent of basal ganglia calcification to be associated with more pronounced neuropsychiatric deficits (Taxer et al., 1986). The initial phase of the disorder is often characterized by obsessive–compulsive states and by affective and schizophrenic symptoms; later stages, by organic brain syndromes of variable severity. These syndromes cannot be explained entirely by basal ganglia changes alone, but suggest the involvement of other cerebral sites, in particular, the frontal lobes. The basal ganglia are heavily interconnected with the frontal cortices via a number of frontostriatal pathways (Alexander et al., 1986). Hence, one can hypothesize that functional cerebral changes in Fahr’s disease are not restricted to the basal ganglia, but may also involve the frontal and temporal lobes. This assumption is supported by Smith et al. (1988), who examined regional cerebral blood flow changes in six patients with non-specified basal ganglia diseases using single photon emission computed tomography with hexamethylpropyleneamine as a tracer. Four of the patients examined showed a prominently decreased regional cerebral blood flow in the basal ganglia matching the distribution of calcifications observed in CT. Moreover, Uygur et al. (1995) reported regional cerebral blood flow decreases not only in the basal ganglia, but also in the frontal lobes and the right parietal lobe in a patient with Fahr’s disease.

In the present study, we examined regional glucose uptake using positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose (FDG) as a tracer in a patient with Fahr’s disease. We were able to combine the better local resolution capacity of PET with neuropsychological testing revealing defined performance deficits in addition to the mere determination of clinical symptoms.

2. Methods

2.1. Patient

2.1.1. Present medical history

The 25-year-old male patient was admitted to the Department of Psychiatry of the University of Heidelberg with organic psychosis of unknown etiology. Born in Sri Lanka as the seventh of 10 children, the patient attended primary school up to 5th grade. In 1988, he asked for asylum in Germany after having lost his mother and five of his siblings in the civil war during the 1980s. One brother died in a car accident in 1989. Starting in 1994, the patient showed behavioral changes including leaving stores without paying for his shopping or driving without having a license. In addition, loss of distance in contact, deterioration of speech and general restlessness of motion were described. Since 1996, the patient presented reduced initiative, indifference and an increased suspicion. Two years later he was committed to a residential home.

After admission, the patient was treated with Pipamperon, a fluorbutyrophenone, resulting in a mild improvement of motor symptoms and perseverations.

A 15-year-old sister was hospitalized in 1995 and 1997, and diagnosed with Fahr’s disease. A severe dementia had developed within 7 years. Beginning in 1989, she showed ‘childlike’ behavioral changes, loss of distance and a cheerful and fearful affect. She was unable to care for her son and daughter and developed intermittent paranoid symptoms as well as severe mnestic deficits. In 1997, the patient was unable to care for herself and computed tomography (CT) revealed a prominent basal ganglia calcification bilaterally (Figs. 1 and 2). Her 9-year-old son and 14-year-old daughter showed normal mental and psychomotor development.

2.1.2. Mental status examination

On admission, the patient was co-operative,
alert and fully oriented. He displayed a friendly but partly inappropriate ‘chummy’ attitude. His movements were awkward with signs of hyperactivity, i.e. he suddenly, and without being able to give a reason, walked across the room in a slouchy and desultory gait. During the examination the patient constantly smiled, even when describing sad or negative events. This inappropriate emotional display made it difficult for the examiner to assess his true affective state. The speech was of simple vocabulary and non-fluent, spoken in a soft and monotonous voice. It was often interrupted by word-finding difficulties, echolalia and verbal perseverations. The patient was easily distractible and did not believe himself to be ill. His memory for commonly known facts and historical events was intact, but he had difficulties in long-term recall. No signs of psychosis such as delusions or hallucinations were observed.

Neurologically, the patient showed intermittent mild dystonic movements of both hands, a mild dysarthria and facial grimacing. The muscular tonus of the extremities was reduced with no signs of circumscribed pareses. Sensibility was
found to be normal for all qualities on standard neurological testing.

2.1.3. Laboratory tests
Blood analysis including copper, coeruloplasmin, ferritin, calcium, phosphorus and parathormon, and analysis of cerebrospinal fluid including Tau protein concentration (for methodological details, see Schönknecht et al., 2000), were normal (168 pg/ml). The ophthalmological examination did not reveal any changes of the cornea. Electroencephalography showed an occipital alpha rhythm with bilateral frontotemporal deceleration.

Computed tomography (CT) revealed a generalized brain atrophy with accentuation of the frontal lobes as well as bilateral basal ganglia calcification in the putamen and in the internal segment of the globus pallidus (Fig. 1).

2.1.4. Neuropsychological evaluation
Due to the patient’s difficulty in speaking and language, non-verbal tests were used for neuropsychological examination (Table 1). The d-2 Attention Performance Test (Brickenkamp, 1994) revealed disturbed selective attention and concentration. On the reduced Wechsler Intelligence Test (Dahl, 1986), the patient exhibited severe impairment regarding abstract reasoning and spatial imagination with numerous verbal perseverations. On the Benton test (Benton, 1996), both figural memory and constructive praxis were equally affected. The Trail-Making Test (Reitan, 1979) revealed severe deceleration in information processing and an inability to execute part II at all, indicating severe deficits in cognitive flexibility. The Clock Drawing Test, which is generally administered as non-verbal screening for dementia (Shulman and Gold, 1993), revealed a severe general cognitive impairment.

2.2. PET data acquisition and analysis
FDG with a high activity concentration (500

Table 1
Neuropsychological test results*

<table>
<thead>
<tr>
<th>Function</th>
<th>Test</th>
<th>Score</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>General intelligence</td>
<td>WIP</td>
<td>General Knowledge: RS 2; PR 2</td>
<td>Far below average</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finding commons: RS 0; PR 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completing pictures: RS 2; PR 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mosaic Test: RS 0; PR 0</td>
<td></td>
</tr>
<tr>
<td>Concentration/selective attention</td>
<td>d-2</td>
<td>Total number of processed signs: 99; PR 0</td>
<td>Far below average</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Percentage of errors: 26.3; PR 0</td>
<td></td>
</tr>
<tr>
<td>Visual memory (instruction A)</td>
<td>Benton test</td>
<td>Total number correct: RS 1; PR 0</td>
<td>Far below average</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of errors: RS 22; PR 0</td>
<td></td>
</tr>
<tr>
<td>Information processing</td>
<td>TMT-A</td>
<td>142 s; PR 0</td>
<td>Far below average</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>TMT-B</td>
<td>&gt; 600 s; PR 0</td>
<td>Far below average</td>
</tr>
<tr>
<td>Constructive praxis/abstract thinking</td>
<td>Clock Drawing Test</td>
<td>RS 4</td>
<td>Impaired</td>
</tr>
<tr>
<td>Degree of cognitive deficits</td>
<td>GDS</td>
<td>RS 6</td>
<td>Severely impaired</td>
</tr>
</tbody>
</table>

*Abbreviations: WIP, reduced Wechsler Intelligence Test; d-2, Attention Performance Test; TMT-A/B, Trail Making Test; GDS, Global Deterioration Scale; RS, raw score; and PR, percentile range.
MBq/ml was produced as described by Oberdorfer et al. (1986). Achieved radiochemical purity was higher than 98%. Scans were taken 45 min after intravenous injection of 160-MBq FDG on the fasted patient (blood glucose = 81 mg/dl) in a quiet environment with eyes closed.

Brain measurements were performed using the latest generation whole-body PET system ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN, USA). The scanner consists of four rings with 72 bismuth germanate block detectors, each covering 155 mm as the axial field of view. Data were in a 3D mode without inter-slice tungsten septa. For the standard acquisition parameters, the total true event sensitivity in the 3D mode is higher by a factor of approximately 4.9 than in the 2D mode (Brix et al., 1997). In the 3D mode, the transaxial resolution is in the range between 4.8 and 4.1 mm. The scanner is equipped with three 68Ge line sources with an activity of approximately 100 MBq each for the acquisition of a transmission and blank scan. Starting a static scan 45 min after injection, emission and transmission data were acquired over 20 and 10 min, respectively. The discretization of the image matrix was 256×256 pixels. Iterative reconstruction of the data was performed using the OSEM algorithm.

For semiquantitative analysis, regions of interest (ROIs) were manually placed on all transaxial slices, covering the normal and hypometabolic brain areas given in Table 2. After correction for radioactive decay ($T_{1/2} = 109.7$ min), FDG uptake was expressed as the standardized uptake value ($SUV$):

$$SUV = \frac{C}{(D/m)}.$$

where $C$ is the tissue activity concentration (kBq/g), $D$ the injected dose (kBq) and $m$ the body weight (grams). Because CT showed a pronounced frontal atrophy, $SUV$’s were corrected for partial volume effect, using recovery coefficients which were previously published for our PET scanner (Adam et al., 1997). Semiquantitative measurements of tracer uptake were obtained by calculating relative $SUV$’s normalized to the global brain metabolism. The respective mean values and S.D.s are based on values obtained in 12 normal controls (11 males, one female, 30 ± 8 years of age) also using a Siemens/CTI HR+ PET scanner (Volkow et al., 2000).

At the time of PET examination, the patient had been treated with 320 mg/day Pipamperon for 5 weeks.

### 3. PET results

Glucose uptake was moderately reduced in the striatum bilaterally; the respective standardized uptake values were at least 15% lower than mean values obtained in controls (Fig. 3). Marked bilateral reductions were found in the frontal and temporo-parietal cortices and the hippocampal area (Fig. 3), while glucose uptake was preserved in other cortical regions such as the sensorimotor and occipital cortices and in the cerebellum. The results of the semiquantitative analysis are given in Table 2.

### 4. Discussion

We report the case of a 25-year-old patient with Fahr’s disease, who presented with frontal lobe syndrome and dementia, both of which had been worsening steadily over the past 5 years. CT
showed a bilateral calcification of the putamen and globus pallidus consistent with Fahr’s disease and a frontally pronounced brain atrophy. In contrast, reduced glucose uptake in PET was not restricted to the basal ganglia, but also involved the frontal, temporal and parietal cortices corresponding to the impaired cognitive flexibility, fig-
differential diagnosis, since clinical symptoms clearly fulfilled the criteria for this disorder suggested by the Lund and Manchester Group (Neary et al., 1998). Basal ganglia changes are not considered to be a common feature of frontotemporal dementia (Jauss et al., 2001). In the present case, the coincidence of dementia with basal ganglia calcification affecting two siblings, the patient’s young age and the hyperkinetic-hypotone syndrome render the diagnosis of frontotemporal dementia rather unlikely.

Recent anatomical studies in animals (Smeets et al., 2000, for review) have demonstrated that vertebrates share a common pattern of basal ganglia organization. The corpus striatum receives numerous fibers from the cerebral cortex and is supposed to represent the entrance to the basal ganglia circuit, whereas the internal segment of the globus pallidus and the substantia nigra constitute the exit with an inhibitory effect on the premotor neurons of the ventral thalamus. Between these structures, a direct monosynaptic and indirect polysynaptic pathway with connections to the external segment of the globus pallidus and the subthalamic nucleus form a balance, which controls movements and muscular tonus.

According to these findings, the hyperkinetic-hypotone syndrome observed in the present case may reflect a reduced activity in the internal segment of the globus pallidus. This assumption is substantiated by animal studies (Cromwell and Berridge, 1994) demonstrating that damage affecting at least 60% of the ventromedial globus pallidus results in a hyperkinetic syndrome; moreover, in the CT study cited above, Taxer et al. (1986) described a close association between basal ganglia changes and both motor and cognitive deficits.

Functional abnormalities did not entirely parallel morphological changes, but were also found in the temporal and parietal lobes which appeared to be rather unaffected in CT. Hence, one may conclude that functional abnormalities may precede morphological changes in the disease process. Alternatively, one may argue that the basal ganglia are heavily interconnected with parietal, temporal, and in particular, the frontal lobes (Alexander et al., 1986; Buchsbaum, 1995). The reduced glucose uptake observed in the respective regions may therefore also reflect secondary deficits due to diminished functions of circuits involving the basal ganglia.

Acknowledgements

The authors are grateful to Ch. Bottmer for her suggestions on the manuscript.

References


